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# THE HUMORAL PRODUCTION OF CARDIAC INFARCTS

BY

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It has long been known that, although desoxycorticosterone itself does not cause nephrocalcinosis, it does produce favourable conditions for the production of this lesion by the concurrent administration of in themselves inactive doses of phosphates (Selye *et al.*, 1945). This typical instance of "conditioning" by a hormone for the potentially pathogenic actions of an otherwise innocuous substance served as a basis for systematic investigations designed to clarify the relationship between the nephrocalcinotic and the other pharmacological actions of steroids (Selye and Bois, 1956a, 1956b).

In the course of more recent studies designed to extend these observations to certain newly synthesized halogenated corticoids, it was accidentally observed that rats treated concurrently with 2α-methyl-9α-chlorocortisol (Me-Cl-COL) and $NaH_2PO_4$ invariably succumbed with the clinical manifestations of acute cardiac death, and necropsy regularly revealed large, yellowish, infarct-like necrotic patches in their myocardium (Selye, 1957a). Subsequent investigations showed that, histologically, these lesions also resemble the true spontaneous cardiac infarcts of man: like the latter, they consist of large, sharply delimited foci in which the myocytes first disintegrate and are then invaded by histiocytes and polymorphonuclear cells. This similarity is further emphasized by the fact that sudden exposure to stress can precipitate the development of such cardiac necroses in rats pretreated with subthreshold doses of phosphate plus Me-Cl-COL or related steroids (Selye and Renaud, 1957a, 1957b). On the other hand, the experimental lesion essentially differs from ordinary infarcts in that there is a constant absence of any histologically demonstrable vascular occlusion. To emphasize both their resemblance to and distinctness from true cardiac infarcts, these lesions have been referred to (with regard to their appearance) as an "infarctoid cardiopathy"; but to distinguish them from infarct-like lesions due to other causes they are also designated (with regard to their causation) as the "phosphate-steroid-cardiopathy" (Selye and Mishra, 1958).

This experimental disease has been the subject of many investigations during the last year, in the hope that the newly discovered interaction between phosphates and steroids might help to elucidate certain problems of cardiac physiology as well as the puzzling but not uncommon cardiac infarcts which occur, without evidence of acute coronary occlusion, in man (Opitz, 1935; Gross and Sternberg, 1939; Meessen, 1944; Büchner, 1955). Therefore, before proceeding with the description of our original observations, it will be necessary to give a brief synopsis of the scattered and polyglot literature concerned with the pathogenesis and clinical implications of the phosphate-steroid-cardiopathy. These may be summarized under the following five headings.

### 1. The Electrolyte Component

Our first task was to establish whether it is really the $PO_4$ moiety of $NaH_2PO_4$ that is of importance in conditioning the cardiac muscle for the necrotizing actions of steroids such as Me-Cl-COL. Experiments on rats indicated that both $NaH_2PO_4$ and $Na_2HPO_4$ (as well as neutral mixtures of both these salts) are highly active in this respect. It was assumed, therefore, that the lesions are not due merely to a change in *p*H induced either by the acid or by the basic phosphate. Since, on the other hand, equimolecular amounts of NaCl, given conjointly with Me-Cl-COL, failed to produce such myocardial necroses, the sodium ion in itself likewise cannot be the responsible conditioning factor. From this it was concluded that, for the production of the phosphate-steroid-cardiopathy, the phosphate ion is the essential part of $NaH_2PO_4$ (Selye and Renaud, 1958a).

Subsequently, it has also been possible to produce similar cardiac lesions by combined treatment with Me-Cl-COL and other inorganic phosphorus compounds such as $NaH_2PO_3$, $Na_2HPO_3$, $NaH_2PO_2$, $Na_4P_2O_6$, $Na_4P_2O_7$, and $(NaPO_3)_6$. It is of interest that only the last two of these salts share with $NaH_2PO_4$ and $Na_2HPO_4$ the property of producing nephrocalcinosis concurrently with the cardiopathy. Hence the development of the cardiac necroses is not merely the consequence of renal calcification (Selye, 1957b). Up to now, only derivatives of phosphoric acid were found to be effective in producing this cardiopathy; yet the specificity of this salt action has still not been fully proved, because meanwhile few other anions have been tested for their ability to produce cardiac necroses when given in combination with steroids.

It is well known that similar cardiac lesions can also occur in rats maintained on potassium-deficient diets (Thomas *et al.*, 1940; Liebow *et al.*, 1941; Follis, 1942). It has been shown, furthermore, that both the phosphate-steroid-cardiopathy and the accompanying nephrocalcinosis can be prevented by oral administration of KCl (Selye and Renaud, 1957a). In view of this, it would have been tempting to postulate that the combined treatment with phosphate and steroid acts through the production of a potassium deficiency. It soon

became evident, however, that the protective effect of KCl is shared not only by $KHSO_4$, $K_2SO_4$, and $CH_3COOK$, but also by $MgCl_2$ and, though to a much lesser extent, even by $CaCl_2$, $NH_4Cl$, and NaCl. These findings suggested that the prophylactic action of KCl is non-specific and perhaps largely due to the accompanying increase in water turnover. However, forced oral administration of water (even when it is given in amounts far greater than those normally taken by the electrolyte-treated animals) exerts little, if any, protective effect against the phosphate-steroid-cardiopathy, while treatment with comparable quantities of an aqueous glucose solution actually aggravates it (Selye and Mishra, 1958). These observations clearly showed that the protective effect of KCl is not entirely specific, but further work will be necessary to determine the characteristics that electrolyte solutions must possess in order to prevent the phosphate-steroid-cardiopathy.

Our next concern was to establish the site of interaction between $NaH_2PO_4$ and those electrolytes that prevent it from causing the cardiopathy and nephrocalcinosis. Of course, the large amounts of $NaH_2PO_4$ that are required for the production of these changes cannot be administered subcutaneously, intravenously, or intraperitoneally. It was noted, however, that if, in rats, a large subcutaneous air bubble is prepared, and increasing concentrations of irritants are injected into its lumen, the wall of the resulting "granuloma pouch" becomes unusually resistant to the necrotizing effects of highly hypertonic solutions. Hence we injected the requisite amount of phosphate into subcutaneous granuloma pouches of Me-Cl-COL-treated rats which simultaneously received either $MgCl_2$ or KCl by mouth. Under these conditions, both $MgCl_2$ and KCl still exerted their customary prophylactic effect (Selye, 1957c). These experiments furnished definite proof that the protective salts do not act by merely inhibiting the absorption of phosphate through some local interaction with the latter in the gastro-intestinal tract.

Almost 30 years ago it was noted that, in rats, certain steroids of the vitamin-D group can produce cardiac necroses with calcification (Selye, 1929a, 1929b). The question now arose whether this type of change could also be influenced by excessive dietary phosphate. Normally, dihydrotachysterol (D.H.T.) produces calcification and necrosis of the cardiac muscle but no inflammatory reaction; however, simultaneous treatment with $NaH_2PO_4$ transforms the character of these lesions, so that a suppurative acute myocarditis results (Selye, 1958). Like the infarctoid cardiopathy, this inflammatory lesion can be prevented by the concurrent administration of KCl (Selye and Renaud, 1958b).

### 2. The Steroid Component

Among 34 steroids that have been tested so far, Me-Cl-COL proved to be most effective in producing phosphate-steroid-cardiopathy. However, 2$\alpha$-methyl-9$\alpha$-fluorocortisol (Me-F-COL) and the two corresponding non-methylated steroids (9$\alpha$-chlorocortisol and 9$\alpha$-fluorocortisol) are likewise very effective in this respect. Among those examined the only halogenated corticoid devoid of this activity is triamcinolone ($\Delta^1$-9$\alpha$-fluoro-16-hydroxycortisol), a highly active glucocorticoid which possesses little or no mineralocorticoid potency. On the other hand, cortisone, a glucocorticoid with little mineralocorticoid activity, is at least as effective in producing phosphate-steroid-cardiopathy as is desoxycorticosterone, although the latter is much more mineralocorticoid than the former (Selye, 1957d; Selye *et al.*, 1957a). It is especially noteworthy that, when given in combination with $NaH_2PO_4$, even cortisol (hydrocortisone), the principal natural glucocorticoid of man, can produce such cardiac changes (Selye *et al.*, 1957a; Selye and de Salcedo, 1958); the same is true of the natural corticoid mixture that is secreted by the adrenals of animals treated with large amounts of corticotrophin (Selye *et al.*, 1957a).

Under our experimental conditions, none of these steroids produced cardiac necroses when they were administered without phosphate supplements, and desoxycorticosterone was singularly ineffective in this respect, even when given with $NaH_2PO_4$. These findings—as well as the relative non-specificity of the protection offered by potassium—make it difficult to evaluate the claim (Darrow and Miller, 1942) that desoxycorticosterone alone (without phosphate) sometimes produces rather similar, though only histologically detectable, cardiac lesions, as a specific result of its hypokalaemic action.

All the steroid hormones that we found to be highly effective in producing the phosphate-steroid-cardiopathy are potent corticoids. However, from the experiments mentioned so far, it was not possible to ascertain whether the cardiotoxic effect is more closely related to the mineralocorticoid or to the glucocorticoid action. Probably both types of activity are important. In experiments in which neither high doses of triamcinolone (a pure glucocorticoid) nor of desoxycorticosterone (a pure mineralocorticoid) produced any marked degree of cardiopathy in $NaH_2PO_4$-sensitized rats, combined treatment with small doses of both these steroids sufficed to induce pronounced and extensive cardiac necroses (Selye, 1957e). It would appear, therefore, that the concurrent action of mineralocorticoids and glucocorticoids is most effective in conditioning the cardiac muscle to the necrotizing action of phosphates. Of course, the previously mentioned active steroids of the vitamin-D group possess no corticoid actions, but when they are given in combination with phosphates the cardiac lesion that they induce is a suppurating myocarditis, essentially distinct from the infarctoid cardiopathy elicited by steroid hormones under similar conditions (Selye, 1958a; Selye and Renaud, 1958b).

### 3. The Stress Component

It is important to distinguish between the infarctoid cardiopathy that is produced gradually by the persistent action of phosphates and steroids, and the sudden eliciting effect of stress to which we made only cursory reference in the introductory paragraph. To clarify the specificity of this eliciting mechanism, rats were briefly treated with small amounts of Me-Cl-COL plus phosphate. Although this pretreatment produced little or no cardiac damage, subsequent exposure to the stress of a neuromuscular effort (induced by strapping the rats on to a board) immediately elicited severe and extensive cardiac necroses in 100% of the experimental animals. Indeed, even in rats pretreated only with Me-Cl-COL without phosphate supplements, such neuromuscular exertion occasionally produced cardiac lesions (Selye and Renaud, 1957b).

It might have been thought that neuromuscular exertion acts specifically (not merely through its stressor effect); but in rats similarly sensitized with threshold doses of Me-Cl-COL plus phosphate a high incidence of massive myocardial necroses could also be elicited by bilateral vagotomy, hot or cold baths, multiple bone fractures, crushing of intestines, quadriplegia (subsequent to transection of motor nerves), or toxic doses of adrenaline (Selye *et al.*, 1957b). Although all stressors are not equally effective in this respect, it is evident that the eliciting mechanism is largely non-specific. The possibility of precipitating infarct-like myocardial lesions by sudden exposure to stressors is especially significant, in view of its obvious clinical implications.

It is interesting that, in preparing the heart for the production of acute infarct-like changes by subsequent exposure to a neuromuscular exertion, cortisol is again more effective than desoxycorticosterone (Selye, 1957f).

### 4. The Question of Species-specificity

The medical implications of all these observations are largely dependent upon the demonstration that the production of such cardiac necroses is not merely a species-specific reaction type peculiar to the rat. It is significant, therefore, that similar cardiac lesions have also been produced by Me-Cl-COL plus $NaH_2PO_4$ in the guinea-pig, hamster, rabbit, and dog (de Salcedo, 1957; de Salcedo and Selye, 1957). Since the principal glucocorticoid of man is cortisol, it is especially noteworthy that extensive myocardial necroses can likewise be produced in primates (rhesus monkeys) by combined treatment with cortisol acetate and $NaH_2PO_4$ (Selye and de Salcedo, 1958). This makes it probable that the cardiac muscle of man is also sensitive to this type of action.

### 5. Relationship to Cardiac Infarcts of Man

Although manifestly similar in their morphological appearance, the lesions of the phosphate-steroid-cardiopathy differ sharply from the true cardiac infarcts of man, in that they cannot be traced to any histologically demonstrable vascular occlusion. Spasms in the larger branches of the coronary arterial system are also unlikely to be involved in the causation of the phosphate-steroid-cardiopathy, because the necroses do not coincide with individual major vascular territories. They may occur in virtually any part of the heart, but we find them most frequently in the thin wall of the right ventricle, as well as in the papillary muscles and the subendocardial layers in both ventricles.

It must be kept in mind, however, that the development of a cardiac infarct depends primarily upon the relationship between the metabolic requirements of the cardiac muscle and its blood supply; hence combined treatment with phosphates and steroids might act by inducing potentially dangerous metabolic changes within the myocardium, so that even physiological variations in the blood supply, which are normally well tolerated, may result in necroses. In this case the precipitating effect of stress could be due either to an additional increase in the demands made upon the cardiac muscle or to temporary variations of the blood supply that are not reflected by any detectable structural change in the coronary vessels. If this concept were correct, the phosphate-steroid-cardiopathy might help to clarify the connexion between those cardiac infarcts of man that are unaccompanied by acute vascular obstructions and the classical infarcts that are due to demonstrable coronary occlusions. All our experiments were performed on healthy young animals with normal cardiac vessels, while spontaneous infarcts tend to occur with the greatest frequency in middle-aged or older men, in whom even a moderate degree of coronary sclerosis may well act as a predisposing factor for metabolic changes similar to those that are induced by combined treatment with phosphates and steroids.

It was thought that in order to elucidate this problem it would be useful, first to produce a moderate amount of coronary sclerosis and hardening (for instance, by pretreatment with D.H.T.), and then to determine whether such an "artificial ageing" of the arterial system can sensitize the heart to the necrotizing effect of subsequent treatment with phosphate and steroid. Over-dosage with a vitamin-D derivative such as D.H.T. tends to cause a rather diffuse sclerosis of the entire coronary system; consequently, if our hypothesis were proved to be correct, it could be expected that after such pretreatment the subsequent administration of phosphate and steroid would affect all parts of the myocardium and would not be restricted to the usual sites of predilection for the localization of the phosphate-steroid-cardiopathy. It is the object of this communication to report upon experiments in which this hypothesis has been verified.

## Materials and Methods

Thirty female Sprague-Dawley rats, with a mean initial body weight of 103 g. (range, 98–109 g.), were subdivided into three equal groups and treated as indicated in the accompanying Table. During the first 10 days (the "pretreatment period") D.H.T. was given to groups II and III, in the form of a microcrystal suspension, at the dose of 300 $\mu$g. in 0.5 ml. of water once daily, by stomach tube. The rats of group I, which were to act as controls, received no such pretreatment. Then followed a rest period of 10 days, during which no treatment was given to any of the groups, but the food intake of the rats in group I was reduced, so as to bring their body weight close to that of the animals in groups II and III, whose growth rate was reduced by the D.H.T. pretreatment. Beginning on the 20th day of the experiment (that is, after 10 days' rest), the rats of groups I and II received 50 $\mu$g. of 2$\alpha$-methyl-9$\alpha$-chlorocortisol (Me-Cl-COL), in the form of microcrystals of its acetate, in 0.2 ml. of water once daily, subcutaneously, and 300 mg. of monosodium phosphate ($NaH_2PO_4.H_2O$), in 2 ml. of water twice daily, by gavage, until termination of the experiment. During this period the rats of group III were untreated.

Throughout the experiment the animals received only the normal laboratory diet: "Purina Fox Chow" and tap-water. On the 30th day the experiment was terminated by killing all survivors with chloroform. The hearts and kidneys were fixed in neutral formalin for subsequent staining with hematoxylin-phloxine (to show general structure) and with von Kossa's silver nitrate technique (for the histochemical demonstration of calcium).

The mortality rate, the mean body weight just before and after Me-Cl-COL plus $NaH_2PO_4$ treatment, as well as the mean intensity of myocardial necrosis, coronary calcification, and coronary obstruction (all arbitrarily graded 0 to 3) are listed with their standard errors in the Table.

## Results

After five to six days of $NaH_2PO_4$ plus Me-Cl-COL treatment, all the rats of group II (pretreated with D.H.T.) became manifestly ill, and 80% of them died with multiple yellowish myocardial foci which were clearly visible on naked-eye inspection.

Upon histological examination, only occasional small spots of myocardial necrosis (some with secondary invasion by histiocytes and a few polymorphonuclear cells) were seen in *group I*. These foci were predominantly localized throughout the substance of the thin wall of the right ventricle, as well as in the papillary muscles and subendocardial strata of both ventricles—that is, in locations typical for the infarctoid cardiopathy. In none of the animals of this group were there any detectable morphological changes in the coronary vessels.

The picture was entirely different in the rats of *group II* which received the same Me-Cl-COL plus $NaH_2PO_4$ treatment but were pretreated with D.H.T. Here myocardial necroses were much more extensive and quite irregularly

*Humoral Production of Cardiac Infarcts*

| Group | Pretreatment | Body Weight before Treatment (g.) | Treatment | Body Weight after Treatment (g.) | Cardiac Lesions (Scale: 0–3) | | | Mortality (%) |
|---|---|---|---|---|---|---|---|---|
| | | | | | Myocardial Necrosis | Coronary Calcification | Coronary Obstruction | |
| I | None | 133±1·5 | Me Cl-COL+$NaH_2PO_4$ | 150±2·1 | 0·9±0·25 | 0 | 0 | 0 |
| II | D.H.T. | 126±3·3 | Me-Cl-COL+$NaH_2PO_4$ | 127±2·4 | 2·9±0·2 | 2·3±0·28 | 2·1±0·2 | 80 |
| III | D.H.T. | 132±3·8 | None | 160±3·8 | 0 | 0·6±0·14 | 0·8±0·14 | 0 |

distributed throughout the myocardium (Figs. 1 and 2). In addition there was intense calcification in virtually all the ramifications of the coronary arterial system. The calcium deposits took the shape of irregularly fragmented blocks which, in many places, appeared to break through the intima into the vascular lumen and also extended into the adventitia. In contact with these calcified masses there was often connective-tissue proliferation; occasionally inflammation and thrombosis were present. In many arteries there developed an intense subintimal oedema, which led to a considerable reduction or virtual obliteration of the vascular lumen (Fig. 3). Such changes are rather reminiscent of the lesions described by Müller (1949), Bredt (1949), Büchner (1955), and others as being characteristic of the acute coronary death that occasionally occurs in young men, especially in soldiers exposed to the stress of battle.

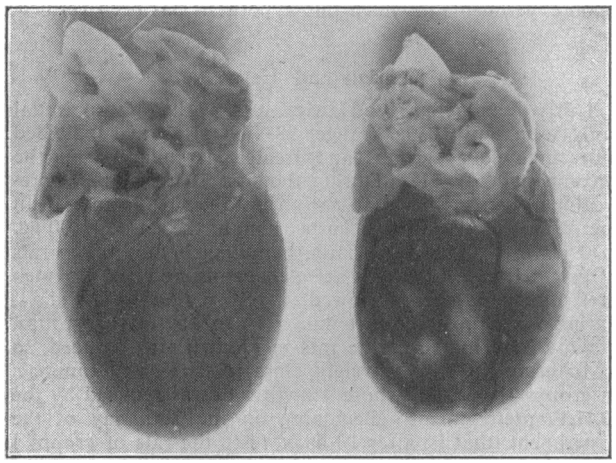

FIG. 1.—Macroscopic appearance of the heart of a rat of group III merely pretreated with D.H.T. (left) in comparison with that of an animal from group II which, after D.H.T.-pretreatment, received Me-Cl-COL plus $NaH_2PO_4$. Note the absence of macroscopically visible changes in the former, while in the latter there are large, irregular light infarcts scattered throughout the substance of both ventricles.

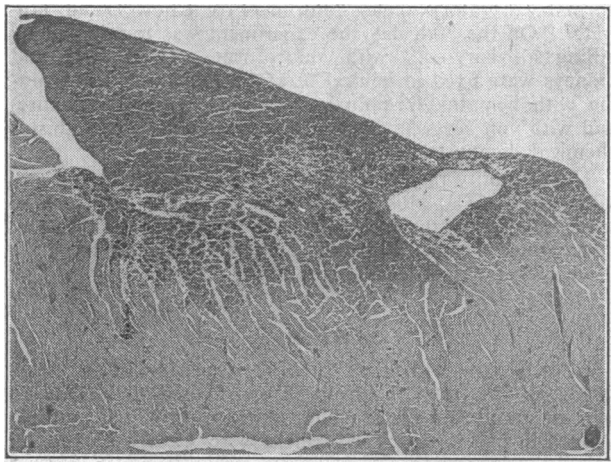

FIG. 2.—Large infarct involving a whole papillary muscle in the left ventricle of a rat from group II. (Haematoxylin-phloxine. ×15.)

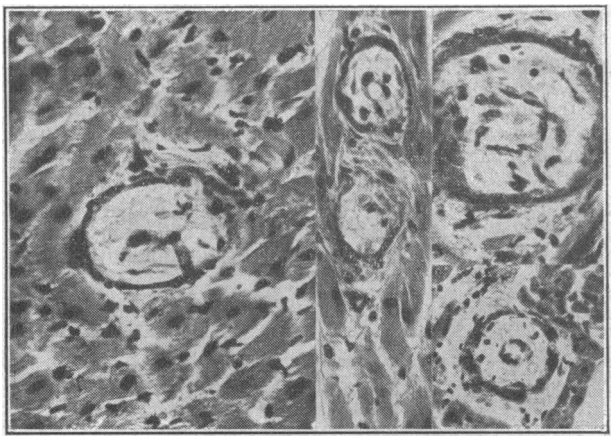

FIG. 3.—Composite picture of several small coronary arteries in a rat of group II. Here, acute subintimal oedema constricts or obliterates the lumen. (Haematoxylin-phloxine. ×230.)

As a result of all these changes the lumen of the entire coronary system, from the largest to the smallest arterial vessels, became greatly narrowed, and in some places it was completely obstructed (Fig. 4). In many large or medium-sized arteries where the obliteration was only subtotal—one or two capillary-sized channels still permitting the passage of blood—it was difficult to differentiate between an excessive acute intima proliferation and the recanalization of an organized thrombus (Fig. 5). In any event, in the coronary system of all the animals in group II (including the two that survived until termination of the experiment) severe mechanical interference with the coronary circulation was quite obvious.

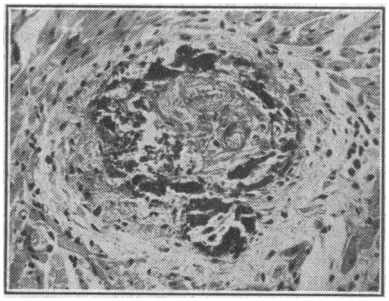

FIG. 4.—Numerous fragmented calcium deposits in the wall, with complete obliteration of the lumen of a coronary artery of a rat from group II. (von Kossa's stain. ×150.)

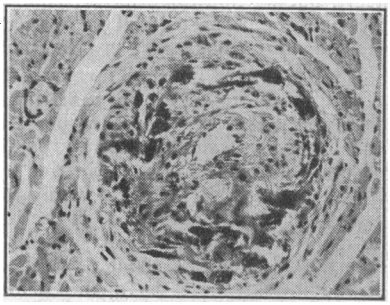

FIG. 5.—Subtotal obliteration of the lumen of another coronary artery from the heart shown in Fig. 4. (von Kossa's stain. ×150.)

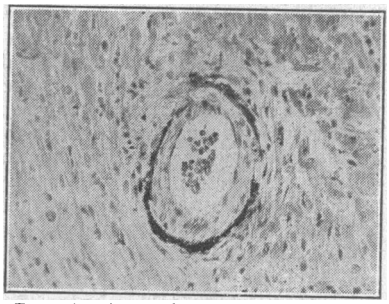

FIG. 6.—One of the most intensely calcified arteries of an animal from group III. Here the calcium deposition is regular (not fragmented) and limited to the media. The intima is moderately thickened, but the lumen remains widely patent and the endothelium intact. (von Kossa's stain. ×150.)

In contrast, the rats of *group III*—that had been similarly pretreated with D.H.T., but received no subsequent treatment with Me-Cl-COL plus $NaH_2PO_4$—revealed only a moderate degree of calcium deposition in the media (Mönckeberg type), limited to a few of the coronary arteries. Even in the most seriously affected vessels (Fig. 6) the calcium deposits formed only thin regular (not fragmented) plaques, which evoked no proliferative reactions in the surrounding tissue, except for occasional slight thickenings in the adjacent intima. Severe obstructions of coronary vessels could not be found in any of the animals of this group.

## Discussion

The typical coronary lesion that usually predisposes for the development of cardiac infarcts in man is an atheromatosis, primarily characterized by lipid deposition and intima proliferation with comparatively little calcification. In our experiments, on the other hand, the D.H.T. pretreatment caused mainly calcium deposition, with little intima proliferation and virtually no lipid deposition. However, in both cases the mechanical effect of the morbid lesions is essentially the same: some degree of constriction and considerable rigidity of the arterial wall. It will be recalled that our object in carrying out these experiments was to verify whether an artificially produced vascular change of this kind would predispose the cardiac muscle to the necrotizing action of subsequent treatment with Me-Cl-COL plus $NaH_2PO_4$. The data presented here show that this was the case. It remains to be established whether interference with the coronary circulation, no matter how produced, would exert a similar sensitizing effect. However, the present experimental series justifies the conclusion that short-term treatment with D.H.T. can so stigmatize the heart that even after clinical recovery the animals remain sensitized to such metabolic derangements as are induced by the subsequent administration of Me-Cl-COL plus $NaH_2PO_4$. In a sense, this stigmatization may perhaps be compared with the effects of ageing and the associated atheromatosis in the human coronary circulation.

Although we suspected that the coronary damage produced by D.H.T. could thus predispose the cardiac muscle to the necrotizing effect of Me-Cl-COL plus $NaH_2PO_4$, it was not expected that the latter treatment would also aggravate the arteriosclerosis itself. It is noteworthy, however, that, under these circumstances, not only cardiac infarction but organic obstruction of the coronary vessels can regularly be produced by humoral means.

Further experiments will have to show whether there is any close relationship between this experimental disease and the spontaneous coronary infarcts of man. It also remains to be seen whether the magnesium and potassium salts that proved to be so eminently effective in the prophylaxis of the phosphate-steroid-cardiopathy will also prevent those types of cardiac necroses that are associated with vascular obstructions.

## Summary

Based on the literature concerning the infarct-like cardiac necroses that are produced by combined treatment with phosphates and steroids (the "phosphate-steroid-cardiopathy"), experiments were designed to determine whether a pre-existent coronary lesion would sensitize the cardiac muscle to this type of damage.

Albino rats were pretreated during 10 days with dihydrotachysterol (D.H.T.), so as to produce mild narrowing and calcification of the coronary arteries. After this, no further treatment was given until all the animals had recovered, as judged by their growth and clinical appearance. Then, combined treatment with $NaH_2PO_4$ plus 2$\alpha$-methyl-9$\alpha$-chlorocortisol (Me-Cl-COL) was initiated at a dose level which in non-pretreated animals caused only occasional microscopical foci of myocardial necrosis, localized in certain areas of predilection. It was found that in the D.H.T.-pretreated rat this same $NaH_2PO_4$ plus Me-Cl-COL treatment produces extensive macroscopically visible patches of necrosis throughout the myocardium and, at the same time, evokes intense, proliferative, and eventually obstructive changes in all parts of the coronary tree.

The possible relationship between this type of experimental disease and the spontaneous coronary infarcts of man is discussed.

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# TREATMENT OF APHTHOUS ULCERATION OF THE MOUTH

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Aphthous ulceration of the mouth is one of the commonest minor maladies. It is probable that within the British Isles more than a million persons are affected with the condition. In its common or *minor* form a single ulcer or a small crop of ulcers appears on the buccal mucous membrane several times a year. The ulcers occur most often on the inside of the cheeks (see illustration) opposite the molar teeth, inside the lips, and occasionally on the tongue, although any part of the mouth or pharynx may be affected. They are painful and interfere with speech and eating, but normally they run a short course and heal in about a week without scarring.

Some patients suffer from a *major* form of aphthous ulceration, which is a much more severe condition. The ulcers are multiple and the patient may be seldom, if ever, free from them over the course of years. When this is so, the disorder ceases to be merely a painful inconvenience and assumes the dimensions of incapacitating illness. Patients thus afflicted with the major form of the condition are fortunately a small minority of the total, but they are nevertheless numerous within the general population.

There is a *special* group of patients showing ulceration of the mouth which is, at any rate superficially,